Novel therapeutic approach: ligands for PPARgamma and retinoid receptors induce apoptosis in bcl-2-positive human breast cancer cells.

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Effective treatment of tumors is often associated with activation of the endogenous apoptosis pathways. We have studied eight breast cancer cell lines (MCF-7, BT20, BT474, MDA-MB-231, MDA-MB-436, SKBR3, T-47D, ZR-75-1) possessing a variety of genetic defects. The clonogenic growth of breast cancer cell lines was inhibited by a ligand for PPARgamma (troglitazone, TGZ) combined with a ligand for either retinoid X receptor (RXR) (LG10069) (4/8 cell lines), RAR (ATRA) (5/8 cell lines) or RAR/RXR and RXR/RXR (9-cis-RA) (5/8 cell lines) independent of their expression of bcl-2, bag-1, ERalpha, and p53. The cell lines (MCF-7, T-47D, ZR-75-1), which expressed both BRCA1 and p27, were extremely sensitive to the inhibitory effect of the combination of TGZ and either ATRA or 9-cis-RA (ED90, 2-5 x 10(-11) M). However, only MCF-7, MDA-MB-231, and ZR-75-1 cells, which expressed a high level of bcl-2 protein, underwent apoptosis when exposed to the combination of TGZ and either ATRA or 9-cis-RA. Importantly, this effect was independent of expression levels of p53, ERalpha, HER-2/neu, bag-1, and BRCA1. Therefore, the combination of ligands for PPARgamma and retinoid receptors may have a therapeutic role for breast cancer.

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